ATTENUATION OF STRESS AND HEMODYNAMIC STABILITY

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While the use of morphine as an anesthetic during coronary artery bypass operations remains controversial, it is still considered favorable for patients undergoing valvular replacement. Lowenstein[1] has stated that large doses of morphine may not produce unconsciousness without supplemental drugs. Others report hypertension and tachycardia during surgical stimulation[2,3] even when the plasma morphine level was three to four times that required for analgesia.[2] This can be explained by the site of action of morphine in the central nervous system.[4] Opiate receptors are more densely located in the substantia gelatinosa of the spinal cord, and the corpus striatum and their numbers in the latter exceed those of the cerebral cortex more than fourfold. The cortex is therefore relatively unsuppressed during narcotic anesthesia, and this can also explain reports of awareness during anesthesia when a narcotic technique is utilized.

Most patients with valvular heart disease have been under the stress of chronic low blood flow and their sympathetic activity may be increased and neurohumoral control of peripheral vascular tone may become augmented.[5] A further increase in peripheral vascular resistance through surgical stimulation when under morphine anesthesia might lead to poor ventricular performance, but stable hemodynamics could be maintained by attenuation of these responses to stress. To test this we undertook a randomized trial of a pharmacologic dose of methylpredonisolone sodium succinate (30 mg./kg.) as a stress-attenuating agent during morphine anesthesia.

MATERIALS AND METHODS

Institutional approval and informed consent were obtained from all patients. The double-blind study was performed in 15 patients undergoing cardiac valve replacement. Patients with complications other than the intrinsic valvular heart disease were excluded from the study. Twelve of the 15 patients had functional Class III to IV acquired valvular heart disease by the New York Heart Association Classification.[6] All medications except sedatives were discontinued 24 hours prior to operation. Preanesthetic medication given one hour before induction of anesthesia was morphine sulfate 0.1 mg./kg. and scopolamine 0.01 mg./kg. intramuscularly. All patients were given oxygen by face mask until arrival in the operating room. In the operating room, 100% oxygen was administered through a tight fitting face mask. Routine preparation included electrocardiogram attachments, blood pressure cuff, peripheral intravenous lines, and radial artery and internal jugular vein cannulation. The arterial and right atrial pressures were continuously monitored and recorded using a Hewlett-Packard multichannel recorder (Model 7754A). Left atrial pressure was also monitored after inserting the catheter prior to the initiation of cardiopulmonary bypass. Measurements were made at three different periods; the control period (preinduction), 60 minutes after the double-blind administration of either drug or placebo and at the termination of operation. Measurements included arterial and mixed venous blood gases and pH, body temperature, cardiac output by the dye dilution method, arterial blood pressure (systolic, diastolic, and mean), atrial pressure, and the heart rate. Cardiac index (L/min./m.^{2}), stroke volume (ml.) and systemic vascular resistance (dyne sec. cm.$^{-5}$) were all calculated according to standard formulas. Throughout anesthesia F_IO_2 of 1.0 was administered. Just prior to the induction of anesthesia, coded drug was administered intravenously over a 10-minute period. The dosages administered were either 30 mg./kg. of methylpredonisolone sodium succinate or 18 mg./kg. of placebo. Four ml. of the coded drugs, either 250 mg. of methylpredonisolone sodium succinate or 150 mg. of placebo, were added to each liter of pump perfusate, which consisted of 2 liters of Normosol®, 500 ml. of whole blood, and 500 ml. of 5% albumin.

Anesthesia was induced with morphine sulfate 1.0 mg./kg. intravenously supplemented with 10 mg. of diazepam. During induction patients were encouraged to breathe deeply to maintain Pa_{CO_2} within normal limits. Endotracheal intubation was facilitated using succinylcholine

and an endotracheal spray with 4 ml. of 4% lidocaine solution. Additional doses of morphine sulfate (10 to 15 mg.) or diazepam (5 mg.) were given if hypertension, tachycardia, or sweating were manifested to maintain anesthesia. Ventilation was mechanically controlled (tidal volume 8-10 ml./kg., 10-12 times/minute). After induction of anesthesia, ventilation was adjusted to keep Pa_{CO_2} within normal limits (36-42). During the second series of measurements, superficial surgery was in progress.

Throughout the procedure, adequate intravascular volume was maintained by infusion of 5% albumin, fresh frozen plasma, or blood according to the right and left atrial pressures and clinical signs. Drug codes were broken at the conclusion of the study, and the patients were divided into control (placebo) and methylpredonisolone sodium succinate treated groups for statistical analysis. Mean and standard error of the mean were calculated for all the values obtained. Student's t-test was used to detect statistical significance of the differences between means. P values of less than 0.05 were considered significant.

RESULTS

The results of the study are shown in Tables I, II, and III.

PATIENTS' DATA

The patients were evenly distributed between the control and methylpredonisolone sodium succinate treated groups with regard to age, sex, and cardiac functional class. In the control group, the age ranged from 28 to 67 years, with a mean of 46 years. There were four men and four women, and six of the eight patients had New York Heart Association Class III and IV heart disease. In the methylpredonisolone sodium succinate group, the age ranged from 39 to 67 years with a mean of 49 years, and there were two men and five women. Six of the seven patients had New York Heart Association Class III to IV heart disease.

HEMODYNAMIC VARIABLES

The control values of two groups did not significantly differ in any of the variables measured. Both groups had low cardiac index and high systemic vascular resistance during this period. Sixty minutes after the administration of the coded drug, while superficial surgery was in progress, the control group demonstrated a significant ($p < 0.05$) reduction

TABLE I: PATIENT DATA

Group	*Patient number*	*Sex*	*Age years*	*Procedures*	*Functional class*
Control	1	M	48	Aortic valve replacement	IV
	2	F	51	Mitral valve replacement	II
	3	M	28	Mitral valve replacement	III
	4	F	62	Aortic valve replacement	III
	5	F	59	Mitral and aortic valve replacement and tricuspid valve annuloplasty	IV
	6	M	67	Aortic valve replacement	III
	7	M	45	Mitral valve replacement	II
	8	M	62	Aortic valve replacement	III
Treated	1	M	39	Mitral valve replacement	III
	2	F	55	Mitral valve replacement	III
	3	F	46	Open mitral commissurotomy and tricuspid valve replacement	III
	4	F	67	Aortic valve replacement	III
	5	F	41	Mitral valve replacement and tricuspid valve annuloplasty	III
	6	M	43	Aortic valve replacement	II
	7	F	53	Mitral valve replacement	III

in cardiac output. Cardiac index and stroke volume associated with a significant increase in systemic vascular resistance ($p < 0.05$) and heart rate ($p < 0.05$). In contrast, the methylpredonisolone sodium succinate group demonstrated no significant change in any of these variables. At the end of the operation, the control group continued to demonstrate significant reduction in cardiac output, cardiac index, stroke volume, and a significant increase in heart rate with a borderline ($p=0.06$) increase in systemic vascular resistance. In the methylpredonisolone sodium succinate group, there were reductions in cardiac output, cardiac index, and stroke volume with an increase in heart rate; however, these changes were not statistically significant.

BLOOD GASES AND pH

In the control group, arterial blood gases and pH remained unchanged throughout surgery except for significant ($p < 0.05$) reduction in PaO_2 at one hour and a significant ($p < 0.05$) increase in $PaCO_2$ at the end of sur-

TABLE II: CHANGES IN HEMODYNAMIC VARIABLES IN PLACEBO AND METHYLPREDONISOLONE TREATED GROUPS.

	Control (placebo)			*MPSS*		
	Preop.	*1 hr.*	*Closure*	*Preop.*	*1 hr.*	*Closure*
CO	3.12 ± 0.33	2.32 ± 0.12*	2.26 ± 0.19*	3.26 ± 0.71	3.27 ± 0.64	2.77 ± 0.35
CI	1.80 ± 0.21	1.33 ± 0.07*	1.33 ± 0.14*	1.96 ± 0.34	1.96 ± 0.30	1.68 ± 0.10
SV	51.3 ± 6.5	33.4 ± 3.4*	27.9 ± 4.3‡	45.6 ± 7.8	43.7 ± 7.9	33.3 ± 2.9
SVR	2287 ± 253	3139 ± 193*	3052 ± 310	2389 ± 404	2561 ± 435	2331 ± 324
MAP	93.6 ± 4.5	100.3 ± 5.3	94.9 ± 4.9	93.1 ± 3.9	101 ± 5.7	83.9 ± 6.0
CVP	11.1 ± 2.2	10.1 ± 2.1	13.1 ± 1.3	12.1 ± 4.4	12.9 ± 3.8	11.1 ± 1.1
HR	65.8 ± 4.2	72.8 ± 5.1†	92.3 ± 11.1*	70.3 ± 3.2	75.1 ± 4.7	83.0 ± 7.0

* $p < 0.05$
† $p < 0.025$
‡ $p < 0.01$

CO = cardiac output L/min., CI = cardiac index L/min./m.^{2}., SV = stroke volume ml., SVR = systemic vascular resistance dyne sec. cm.$^{-5}$, MAP = mean arterial pressure mm. Hg., CVP = central venous pressure, HR = heart rate beats/min.

TABLE III:

CHANGES IN BLOOD GASES AND pH IN PLACEBO AND METHYLPREDONISOLONE SODIUM SUCCINATE TREATED GROUPS.

	Preop.	*1 hr.*	*Closure*	*Preop.*	*1 hr.*	*Closure*
PaO_2	398 ± 22	370 ± 19*	327 ± 47	452 ± 6	363 ± 50	317 ± 45**
$PaCO_2$	39.8 ± 1.8	43.5 ± 1.9	47.0 ± 2.2*	37.6 ± 2.2	44.7 ± 2.7*	43.3 ± 2.8
Ph	7.41 ± 0.01	7.38 ± 0.02	7.37 ± 0.02	7.42 ± 0.01	7.35 ± 0.01†	7.37 ± 0.03
PVO	48.5 ± 1.6	46.5 ± 2.1	38.8 ± 1.7‡	52.8 ± 5.7	51.7 ± 6.1	41.3 ± 2.6
$PVCO_2$	49.4 ± 1.3	51.8 ± 1.7	54.5 ± 1.5*	43.7 ± 2.0	51.0 ± 2.7*	49.1 ± 2.2
Ph	7.38 ± 0.01	7.34 ± 0.02*	7.33 ± 0.02	7.38 ± 0.01	7.33 ± 0.02	7.32 ± 0.03

* $p < 0.05$
† $p < 0.025$
‡ $p < 0.01$

gery. Venous blood gases and pH demonstrated a significant ($p < 0.05$) decrease in pH with no changes in $P_{V}CO_2$ at one hour. At the end of operation, there was a significant ($p < 0.05$) increase in $P_{V}CO_2$ with borderline decrease ($p < 0.06$) in pH. $P_{V}O_2$ decreased significantly ($p < 0.01$).

In contrast to the control group, in the methyl predonisolone sodium succinate group there was a significant ($p < 0.05$) increase in $PaCO_2$ with a concomitant decrease ($p < 0.02$) in pH at one hour, and at the end of operation there was a significant ($p < 0.02$) decrease in PaO_2. Venous blood gases and pH showed also a significant ($p < 0.05$) increase in $P_{V}CO_2$ with a concomitant decrease in pH ($p < 0.05$). At the end of surgery there were no significant changes in any of the variables and $P_{V}O_2$ was well maintained.

DISCUSSION

Philbin et al.[6] demonstrated that during morphine anesthesia with surgical stimulation plasma antidiuretic hormone levels increased significantly and they suggested that this increase is a stress response. They also stated that antidiuretic hormone levels are beyond the physiological range for antidiuretic action on the kidney and may cause a vasopressor response. On the other hand, Balasaroswathi et al.[7] demonstrated that plasma catecholamines are significantly elevated during surgery under morphine anesthesia in cardiac patients. These studies simply indicated that stress response to surgical stimulation are not well suppressed by morphine anesthesia and thus high level of stress hormones are present in plasma. Altura and Altura[8-10] demonstrated that when methylpredonisolone sodium succinate is administered intravenously in a pharmacologic dose to rats in shock, it effectively restores the severely constricted arterioles to near normal state. They also demonstrated in their study using *in vivo* (arterioles) as well as *in vitro* (arteries) preparations that pharmacologic doses of methylpredonisolone sodium succinate inhibited epinephrine, norepinephrine, antidiuretic hormone, serotonin, and angiotensin induced contractions. Matsuki et al.[11] reported that methylpredonisolone sodium succinate (30 mg./kg.) reduced increased levels of plasma antidiuretic hormone usually associated with hemorrhage and cardiopulmonary bypass. They suggested that methylpredonisolone sodium succinate could prevent secondarily peripheral vasoconstriction.

The results of our study demonstrated that the hemodynamics in the patients who received methylpredonisolone sodium succinate (30 mg./

kg.) intravenously were more stable than those of the patients in the control group. The most logical explanation for this finding is that methylpredonisolone sodium succinate prevented the increase in systemic vascular resistance produced by surgical stimulation and thus allowed better maintenance of the cardiac output. It has become increasingly clear that cardiac function is critically dependent upon the outflow resistance against which the ventricle must pump.[12-14] Vasodilator drugs have been demonstrated to shift the function curve upward and to the left which in turn improves low cardiac output in patients with valvular disease.[15]

Of the various agents employed clinically, the role of methylpredonisoline sodium succinate remains controversial. However, our study demonstrated that methylpredonisolone sodium succinate prevented an increase in systemic vascular resistance due to surgical stimulation. We did not measure hormonal or metabolic changes in this study. Therefore, the precise mechanism by which methylpredonisolone sodium succinate acted to prevent an increase in systemic vascular resistance is not clear. Recently, Matsuki et al.[16] clearly demonstrated that administration of steroids during narcotic anesthesia reduced the levels of vasoactive hormones such as antidiuretic hormones and catecholamines, resulting in better peripheral circulation. Thus, administration of steroids during surgery may be beneficial for circulatory homeostasis in valvular surgical patients under narcotic anesthesia. No complications were observed in patients who received a pharmacological dose of methylpredonisolone sodium succinate.

During the course of valvular surgery, the physiological dead space to tidal volume ratio has been reported to be elevated (0.5 to 0.6),[17] and methylpredonisolone sodium succinate appeared to enhance such changes as demonstrated by the significant increase in $PaCO_2$ with a significant decrease in pH at one hour. These changes, together with the concomitant increase in P_VCO_2 and decrease in venous pH, suggested there may also be vasodilation of the pulmonary vascular bed,[18] which in turn caused uneven distribution of pulmonary perfusion and an increase in dead space.

SUMMARY

During morphine anesthesia, hypertension and tachycardia are often evident with surgical stimulation. To attenuate those undesirable responses to surgery in cardiac surgical patients, a pharmacologic dose of

methylpredonisolone sodium succinate (30 mg./kg.) was used. This double-blind study was performed in 15 patients undergoing valvular surgery; eight patients received placebo drugs and seven received methylpredonisolone sodium succinate intravenously before induction of anesthesia. Hemodynamic variables and blood gases were determined before induction, one hour after the coded drugs were given and at the end of operation. The control group (placebo) had a significantly ($p < 0.05$) decreased cardiac output with a concomitant increase ($p < 0.05$) in systemic vascular resistance and heart rate at one hour and the end of operation. In contrast, methylpredonisolone sodium succinate treated patients had stable hemodynamics throughout operation. A pharmacologic dose of methylpredonisolone sodium succinate was found to be effective by attenuated stress response to operation when using morphine anesthesia.

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